Preparation of fluoromethyl-substituted heterocycles

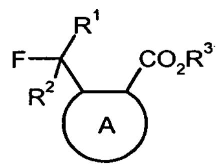
The present invention relates to a novel process for preparing fluoromethyl-substituted heterocycles by reacting the corresponding chloromethyl-substituted compound with a fluorinating agent.

It is already known that 3-(difluoromethyl)- and 3-(fluorodichloromethyl)-1-methyl-1H-pyrazole-4-carboxylic esters can be obtained by reacting the correspondingly halogenated 2-(ethoxymethylene)methyl acetoacetate with methylhydrazine (cf. WO 92/12970 and WO 93/11117).

It is also known that 5-chloropyrazole-4-carboxaldehyde derivatives can be reacted with potassium fluoride in dimethylformamide to give the corresponding 5-fluoro compound (cf. WO 93/11117).

The conversion of heterocycles which are substituted by mono-, di- or trichloromethyl to fluorinated analogues is known hitherto only for pyridine derivatives. Since chlorinated precursors are frequently more readily available than the corresponding fluorine compounds for the preparation of heterocycles, there is a need for a process which allows chlorinated heterocycles to be directly fluorinated.

The present invention thus provides a process for preparing fluoromethyl-substituted heterocycles of the formula (I)



(I)

in which

R^1 is hydrogen, fluorine or chlorine,

R^2 is hydrogen, fluorine or chlorine,

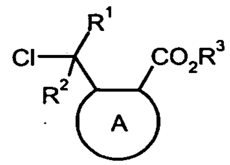
R^3 is C_1-C_6-alkyl,

A is a 5-membered heterocycle selected from the group of pyrazole which is substituted by R^4 in the 1-position, thiazole which is substituted by R^4 in the 2-position and oxazole which is substituted by R^4 in the 2-position,

R^4 is C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-alkylthio-C_1-C_4-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl or phenyl,

characterized in that

a) chloromethyl-substituted heterocycles of the formula (II)



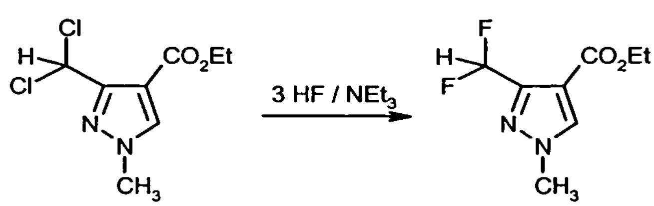
(II)

in which R^1, R^2, R^3 and A are each as defined above

are converted in the presence of a fluorinating agent and optionally in the presence of a diluent.

Surprisingly, the fluoromethyl-substituted heterocycles of the formula (I) can be prepared with good yields in high purity and selectivity under the inventive conditions. Although the preparation of trifluoromethyl-, difluoromethyl- or monofluoromethyl-substituted aromatic compounds from the correspondingly chlorinated compounds by halogen exchange is known for phenyl- and some 3-trihaloalkylpyridine derivatives, it is necessary in these processes to employ severe conditions such as the use of HF, high temperatures and pressure. Under these reaction conditions, those skilled in the art, in the case of pyrazole, thiazole and other heterocyclic compounds which are substituted by trichloromethyl or by the more sensitive and less stable dichloromethyl, would expect the decomposition of the heterocycle (for example by polymerization, hydrolysis or the formation of acids and aldehydes). This decomposition process is even accelerated when, for example, a dichloromethyl group is conjugated directly with an electron pair of a nitrogen atom, as is the case for 3-haloalkyl-substituted pyrazoles. In addition, the fluorination of compounds having a substituent in the ortho-position, especially when it is the large and electron-withdrawing carboxylic ester group, is distinctly more difficult to carry out for steric and electronic reasons. This is because the carboxylic ester group is normally hydrolysed under strongly acidic conditions (for example when HF or its derivatives are used) and forms a ring with the adjacent trichloromethyl or dichloromethyl group. It is all the more surprising that the fluoromethyl-substituted heterocycles of the formula (I) can be obtained in good yields by the process according to the invention.

When, for example, ethyl 3-(dichloromethyl)-1-methyl-1H-pyrazole-4-carboxylate is used as a starting material and triethylamine (tris)hydrofluoride as the fluorinating agent, the process according to the invention (a) may be illustrated by the following scheme.



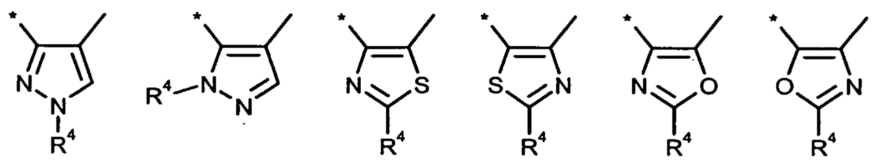
The chloromethyl-substituted heterocycles used as starting materials when carrying out the process according to the invention are generally defined by the formula (II). The substituents have the following preferred definitions:

R^1 is preferably hydrogen, fluorine or chlorine.

R^2 is preferably hydrogen, fluorine or chlorine.

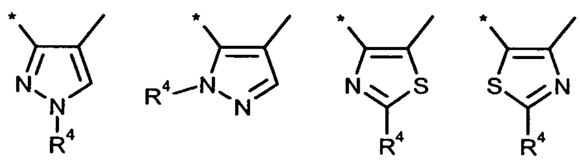
R^3 is preferably C_1-C_4-alkyl, more preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl, most preferably methyl or ethyl.

A is preferably a 5-membered heterocycle selected from the group of



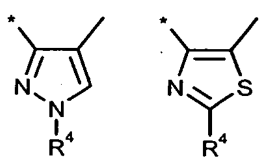
,

more preferably a 5-membered heterocycle selected from the group of



,

most preferably a 5-membered heterocycle selected from the group of



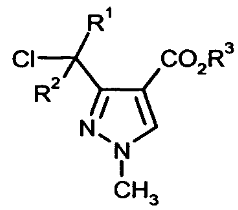
,

where in each case the bond marked by * is joined to the -CClR^1R^2 group and the other bond to the ester group,

R^4 is preferably methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopentyl, cyclohexyl or phenyl, more preferably methyl, ethyl, isopropyl or phenyl, most preferably methyl.

The starting material used is preferably a chloromethyl-substituted heterocycle of the formula (II) in which R^1 is chlorine and R^2 is hydrogen.

Particularly preferred starting materials of the formula (II) are chloromethyl-substituted heterocycles of the formula (II-a)

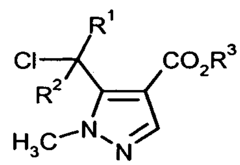


(II-a)

in which R^1, R^2 and R^3 are each as defined above.

Very particular preference is given to compounds of the formula (II-a) in which R^1 is chlorine, R^2 is hydrogen and R^3 is methyl or ethyl.

Particularly preferred starting materials of the formula (II) are likewise chloromethyl-substituted heterocycles of the formula (II-b)

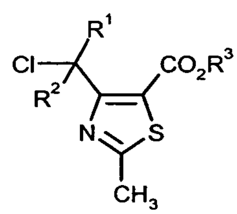


(II-b)

in which R^1, R^2 and R^3 are each as defined above.

Very particular preference is given to compounds of the formula (II-b) in which R^1 is chlorine, R^2 is hydrogen and R^3 is methyl or ethyl.

Particularly preferred starting materials of the formula (II) are likewise chloromethyl-substituted heterocycles of the formula (II-c)

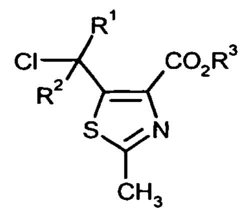


(II-c)

in which R^1, R^2 and R^3 are each as defined above.

Very particular preference is given to compounds of the formula (II-c) in which R^1 is chlorine, R^2 is hydrogen and R^3 is methyl or ethyl.

Particularly preferred starting materials of the formula (II) are likewise chloromethyl-substituted heterocycles of the formula (II-d)



(II-d)

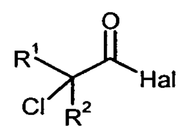
in which R^1, R^2 and R^3 are each as defined above.

Very particular preference is given to compounds of the formula (II-d) in which R^1 is chlorine, R^2 is hydrogen and R^3 is methyl or ethyl.

Some chloromethyl-substituted heterocycles of the formula (II) are known (cf. WO 92/12970, WO 93/11117 and The Chemistry of Heterocyclic Compounds: Thiazole and its derivatives, Jaques Metzger (ed.), Vol. 34, Part 1-3, John Wiley and Sons, New York, 1979).

3-Halomethyl-1H-pyrazole-4-carboxylic esters can be prepared by

b) reacting acid halides of the formula (III)



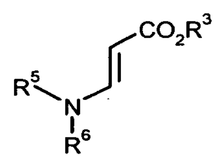
(III)

in which

R^1 and R^2 are each as defined above,

Hal is fluorine, chlorine or bromine,

with dialkylaminoacrylic esters of the formula (IV)



(IV)

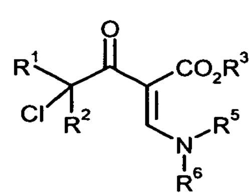
in which

R^3 is as defined above,

R^5 and R^6 are each independently C_1-C_4-alkyl

in a water-immiscible organic solvent (for example toluene) in the presence of a base (for example sodium hydroxide or pyridine),

and reacting the thus obtained 2-dihaloacyl-3-aminoacrylic esters of the formula (V)



(V)

in which R^1, R^2, R^3, R^5 and R^6 are as each as defined above
with hydrazine derivatives of the formula (VI)

$$R^4\text{—NH—NH}_2 \qquad \text{(VI)}$$

in which R^4 is as defined above
in the presence of a diluent (for example toluene).

The process (a) according to the invention is carried out in the presence of a fluorinating agent. Useful for this purpose are all customary fluorinating agents for such reactions. Preference is given to using, for example, alkali metal fluorides such as sodium fluoride, potassium fluoride and caesium fluoride, cobalt(III) fluoride, halogen fluorides, antimony fluorides, molybdenum fluoride, hydrogen fluoride, hydrogen fluoride/pyridine mixtures, tertiary ammonium hydrofluorides or trialkylamine hydrofluorides of the general formula n HF / $N(Alk)_3$ (where n is 1, 2, or 3, preferably 2 or 3, and Alk is C_1-C_4-alkyl, preferably ethyl or n-butyl). Particular preference is given to using 3 HF / $N(Et)_3$ (Franz reagent), 3 HF / $N(n\text{-}Bu)_3$ and HF/pyridine (Olah's reagent). Very particular preference is given to using 3 HF / $N(Et)_3$ (Franz reagent) or 3 HF / $N(n\text{-}Bu)_3$.

The process according to the invention is optionally carried out in the presence of a diluent. Preference is given to using nitriles such as acetonitrile; halogenated hydrocarbons, for example chlorobenzene, dichlorobenzene, dichloromethane, chloroform, tetrachloromethane, dichloroethane, trifluorochloromethane, 1,1,2-trifluoro-1,2,2-trichloroethane, 1,1,1-trifluoro-2,2,2-trichloroethane or trichloroethane; aromatic hydrocarbons, for example petroleum ether, hexane, heptane, cyclohexane, methylcyclohexane, benzene, toluene, xylene or decalin; ethers such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, methyl tert-amyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxyethane or anisole; diethylene glycol. Particular preference is given to using acetonitrile, toluene, chlorobenzene, trifluorochloromethane, 1,1,2-trifluoro-1,2,2-trichloroethane, 1,1,1-trifluoro-2,2,2-trichloroethane, dioxane or diethylene glycol.

When carrying out the process according to the invention, it is possible to work within a relatively wide temperature range. In general, working temperatures are 80°C to 170°C or in the range of 20°C to 170°C, preferably 120°C to 150°C or 100°C to 150°C.

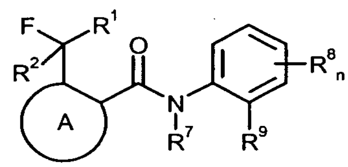
The process according to the invention is generally carried out under atmospheric pressure, However, it is also possible to work under elevated or reduced pressure, generally between 0.1 bar and 50 bar, preferably between 1 bar and 10 bar.

The reaction time is not critical and may be selected depending on the batch size within a relatively wide range of 1 h to 20 h, preferably of 6 h to 12 h.

When carrying out the process according to the invention, for 1 mol of chloromethyl-substituted heterocycles of the formula (II), generally between 1 mol and 3 mol of bound HF, preferably between 1 mol and 1.5 mol, of fluorinating agent are used per chlorine atom.

The fluoromethyl-substituted heterocycles of the formula (I) which can be prepared by the process according to the invention are valuable precursors for the preparation of halomethyl-substituted pyrazolyl-, thiazolyl- and oxazolylcarboxamides which constitute active fungicidal ingredients (cf. WO 03/070705).

For example, fungicidally active carboxamides of the formula (VII)



(VII)

in which

R^1, R^2 and A are each as defined above,

R^7 is hydrogen, C_1-C_8-alkyl, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_8-cycloalkyl; C_1-C_6-haloalkyl, C_1-C_4-haloalkylthio, C_1-C_4-haloalkylsulphinyl, C_1-C_4-haloalkylsulphonyl, halo-C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_8-halocycloalkyl having in each case 1 to 9 fluorine, chlorine and/or bromine atoms; formyl, formyl-C_1-C_3-alkyl, (C_1-C_3-alkyl)carbonyl-C_1-C_3-alkyl, (C_1-C_3-alkoxy)carbonyl-C_1-C_3-alkyl; halo-(C_1-C_3-alkyl)carbonyl-C_1-C_3-alkyl, halo-(C_1-C_3-alkoxy)carbonyl-C_1-C_3-alkyl having in each case 1 to 13 fluorine, chlorine and/or bromine atoms; (C_1-C_8-alkyl)carbonyl, (C_1-C_8-alkoxy)carbonyl, (C_1-C_4-alkoxy-C_1-C_4-alkyl)carbonyl, (C_3-C_8-cycloalkyl)carbonyl; (C_1-C_6-haloalkyl)carbonyl, (C_1-C_6-haloalkoxy)carbonyl, (halo-C_1-C_4-alkoxy-C_1-C_4-alkyl)carbonyl, (C_3-C_8-halocycloalkyl)carbonyl having in each case 1 to 9 fluorine, chlorine and/or bromine atoms; or $-C(=O)C(=O)R^{10}$, $-CONR^{11}R^{12}$ or $-CH_2NR^{13}R^{14}$,

R^8 is hydrogen, fluorine, chlorine, methyl, isopropyl, methylthio or trifluoromethyl,

n is 1, 2, 3 or 4, preferably 1 or 2,

R^9 is optionally mono- to pentasubstituted phenyl having identical or different substituents which are selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_2-haloalkyl or C_1-C_2-haloalkoxy having in each case 1 to 5 fluorine, chlorine and/or bromine atoms, hydroxyimino-C_1-C_4-alkyl, C_1-C_4-alkoxyimino-C_1-C_4-alkyl, C_1-C_4-haloalkoxyimino-C_1-C_4-

alkyl, or, in the case of two adjacent substituents, from difluoromethylenedioxy or tetrafluoroethylenedioxy;

or is C_3-C_{10}-cycloalkyl or C_3-C_{10}-bicycloalkyl which is in each case optionally mono- to tetrasubstituted, identically or differently, by halogen and/or C_1-C_4-alkyl;

or unsubstituted C_2-C_{20}-alkyl, or C_1-C_{20}-alkyl which is mono- or polysubstituted, identically or differently, by fluorine, chlorine, bromine, iodine and/or C_3-C_6-cycloalkyl, in which case the cycloalkyl moiety may itself optionally be mono- to tetrasubstituted, identically or differently, by fluorine, chlorine, bromine, iodine, C_1-C_4-alkyl and/or C_1-C_4-haloalkyl;

or is C_2-C_{20}-alkenyl or C_2-C_{20}-alkynyl which is in each case optionally mono- or polysubstituted, identically or differently, by fluorine, chlorine, bromine, iodine and/or C_3-C_6-cycloalkyl in which case the cycloalkyl moiety may itself optionally be mono- to tetrasubstituted, identically or differently, by fluorine, chlorine, bromine, iodine, C_1-C_4-alkyl and/or C_1-C_4-haloalkyl;

R^{10} is hydrogen, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_8-cycloalkyl; C_1-C_6-haloalkyl, C_1-C_6-haloalkoxy, halo-C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_8-halocycloalkyl having in each case 1 to 9 fluorine, chlorine and/or bromine atoms,

R^{11} and R^{12} are each independently hydrogen, C_1-C_8-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_8-cycloalkyl; C_1-C_8-haloalkyl, halo-C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_8-halocycloalkyl having in each case 1 to 9 fluorine, chlorine and/or bromine atoms,

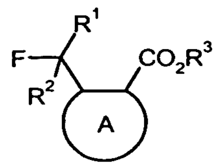
R^{11} and R^{12} are also, together with the nitrogen atom to which they are bonded, a saturated heterocycle having 5 to 8 ring atoms which is optionally mono- or polysubstituted, identically or differently, by halogen or C_1-C_4-alkyl, and the heterocycle may contain 1 or 2 further, nonadjacent heteroatoms from the group of oxygen, sulphur and NR^{15},

R^{13} and R^{14} are each independently nitrogen atom, C_1-C_8-alkyl, C_3-C_8-cycloalkyl; C_1-C_8-haloalkyl, C_3-C_8-halocycloalkyl having in each case 1 to 9 fluorine, chlorine and/or bromine atoms,

R^{13} and R^{14} are also, together with the nitrogen atom to which they are bonded, a saturated heterocycle having 5 to 8 ring atoms which is optionally mono- or polysubstituted, identically or differently, by halogen or C_1-C_4-alkyl, and the heterocycle may contain 1 or 2 further, nonadjacent heteroatoms from the group of oxygen, sulphur and NR^{15},

R^{15} is hydrogen or C_1-C_6-alkyl

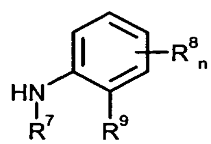
are obtained by hydrolyzing fluoromethyl-substituted heterocycles of the formula (I)



(I)

in which R^1, R^2, R^3 and A are each as defined above

in the presence of a base and optionally in the presence of a diluent, and subsequently either converting the free acid to the corresponding acid chloride in the presence of a chlorinating agent and optionally in the presence of a diluent or reacting the free acid directly with aniline derivatives of the formula (VIII)



(VIII)

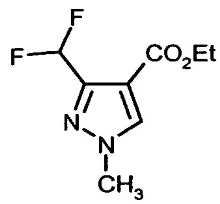
in which R^7, R^8, n and R^9 are each as defined above

optionally in the presence of a catalyst, optionally in the presence of a condensing agent, optionally in the presence of an acid binding agent and optionally in the presence of a diluent.

The inventive preparation of fluoromethyl-substituted heterocycles of the formula (I) is described in the examples which follow, which further illustrate the above description. However, the examples should not be interpreted in a restrictive manner.

Preparative examples

Example 1

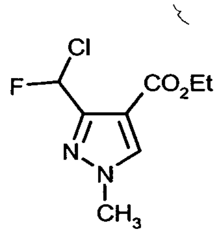


Ethyl 3-(dichloromethyl)-1-methyl-1H-pyrazole-4-carboxylate (37.9 g, 0.16 mol) and triethylamine tris(hydrofluoride) (80 g, 0.49 mol) were heated in an autoclave at 145°C for 8 h. The reaction mixture was then diluted with 200 ml of water. The precipitated product was filtered off, washed and dried.

28.5 g (87% of theory) of ethyl 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate having a melting point of 43-46°C were obtained.

^{1}H NMR ($CDCl_3$): δ = 1.35 (t, 3H); 3.96 (t, 3H); 4.31 (q, CH_2); 7.10 (t, CF_2H); 7.90 (s, 1H) ppm.
^{19}F NMR ($CDCl_3$): δ = −117.2 (d, J = 55.4 Hz) ppm.

Example 2

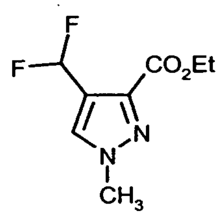


37.9 g (0.16 mol) of ethyl 3-(dichloromethyl)-1-methyl-1H-pyrazole-4-carboxylate and 80 g (0.49 mol) of triethylamine tris(hydrofluoride) were heated in an autoclave at 120°C for 8 h. The reaction mixture was then diluted with 200 ml of water and the product extracted with ethyl acetate. The desired product was removed by chromatography from ethyl 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate and isolated.

20 g (56% of theory) of ethyl 3-(fluorochloromethyl)-1-methyl-1H-pyrazole-4-carboxylate were obtained.

^{19}F NMR ($CDCl_3$): δ = −133.8 (d, J= 47.5 Hz) ppm.

Example 3



37.9 g (0.16 mol) of ethyl 4-(dichloromethyl)-1-methyl-1H-pyrazole-3-carboxylate and 80 g (0.49 mol) of triethylamine tris(hydrofluoride) were heated in an autoclave at 160°C for 8 h. The reaction mixture was then diluted with 200 ml of water and the product extracted with ethyl acetate. The desired product was purified by chromatography and isolated.

26.8 g (75% of theory) of ethyl 4-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxylate having a melting point of 30-31°C were obtained.

^{1}H NMR ($CDCl_3$): δ = 1.37 (t, 3H); 4.07 (t, 3H); 4.31 (q, CH_2); 7.49 (t, CF_2H); 7.86 (s, 1H) ppm.

^{19}F NMR ($CDCl_3$): δ = −117.2 (d, J = 54.7 Hz) ppm.